Novo Nordisk

PRODUCT INFORMATION

NorditropinÒ cartridges

Somatropin (rDNA origin) injection
5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL

DESCRIPTION

Norditropin® is the Novo Nordisk Pharmaceuticals, Inc. registered trademark for somatropin, a polypeptide hormone of recombinant DNA origin. The hormone is synthesized by a special strain of *E. coli* bacteria that has been modified by the addition of a plasmid which carries the gene for human growth hormone. Norditropin® contains the identical sequence of 191 amino acids constituting the naturally occurring pituitary human growth hormone with a molecular weight of about 22,000 Daltons.

Norditropin® cartridges are supplied as solutions in ready-to-administer cartridges with a volume of 1.5 mL.

Each **Norditropin® cartridge** contains the following:

Component	**5 mg/1.5 mL**	**10 mg/1.5 mL**	**15 mg/1.5 mL**
Somatropin	5 mg	10 mg	15 mg
Histidine	1 mg	1 mg	1.7 mg
Poloxamer 188	4.5 mg	4.5 mg	4.5 mg
Phenol	4.5 mg	4.5 mg	4.5 mg
Mannitol	60 mg	60 mg	58 mg
HCl/NaOH	q.s.	q.s.	q.s.
Water for Injection	ad 1.5 mL	ad 1.5 mL	ad 1.5 mL

CLINICAL PHARMACOLOGY

a. Tissue Growth

The primary and most intensively studied action of somatropin is the stimulation of linear growth. This effect is demonstrated in patients with somatropin deficiency.

1. Skeletal growth – the measurable increase in bone length after administration of somatropin results from its effect on the cartilaginous growth areas of long bones. Studies *in vitro* have shown that the incorporation of sulfate into proteoglycans is not due to a direct effect of somatropin, but rather is mediated by the somatomedins or insulin-like growth factors (IGF). The somatomedins, among them somatomedin C, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissue. Somatomedin C is low in the serum of hypopituitary dwarfs and hypophysectomized humans or animals, but its presence can be demonstrated after treatment with somatropin.

2. Cell growth – it has been shown that the total number of skeletal muscle cells is markedly decreased in short stature children lacking endogenous somatropin compared with normal children, and that treatment with somatropin results in an increase in both the number and size of muscle cells.

3. Organ growth – somatropin influences the size of internal organs, and it also increases red cell mass.

b. Protein Metabolism
Linear growth is facilitated in part by increased cellular protein synthesis. This synthesis and growth are reflected by nitrogen retention which can be quantitated by observing the decline in urinary nitrogen excretion and blood urea nitrogen following the initiation of somatropin therapy.

c. Carbohydrate Metabolism
Hypopituitary children sometimes experience fasting hypoglycemia that may be improved by treatment with somatropin. In healthy subjects, large doses of somatropin may impair glucose tolerance. Although the precise mechanism of the diabetogenic effect of somatropin is not known, it is attributed to blocking the action of insulin rather than blocking insulin secretion. Insulin levels in serum actually increase as somatropin levels increase.

d. Fat Metabolism
Somatropin stimulates intracellular lipolysis, and administration of somatropin leads to an increase in plasma free fatty acids, cholesterol, and triglycerides. Untreated growth hormone deficiency is associated with increased body fat stores including increased subcutaneous adipose tissue. On somatropin replacement a general reduction of fat stores and of subcutaneous tissue in particular takes place.

e. Mineral Metabolism
Administration of somatropin results in the retention of total body potassium and phosphorus and to a lesser extent sodium. This retention is thought to be the result of cell growth. Serum levels of phosphate increase in patients with growth hormone deficiency after somatropin therapy due to metabolic activity associated with bone growth. Serum calcium levels are not altered. Although calcium excretion in the urine is increased, there is a simultaneous increase in calcium absorption from the intestine. Negative calcium balance, however, may occasionally occur during somatropin treatment.

f. Connective Tissue Metabolism
Somatropin stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

g. Pharmacokinetics
A 180-min IV infusion of Norditropin® (33 ng/kg/min) was given to 9 GHD patients. A mean (±SD) hGH steady-state serum level of approximately 23.1 (±15.0) ng/mL was reached at 150 min and a mean clearance rate of approximately 2.3 (±1.8) mL/min/kg or 139 (±105) mL/min for hGH was obtained. Following infusion, serum hGH levels had a biexponential decay with a terminal elimination half-life ($T_{1/2}$) of approximately 21.1 (±5.1) min.

In a study conducted in 18 GHD adult patients, where a SC dose of 0.024 mg/kg or 3 IU/m^2 was given in the thigh, the mean (±SD) C_{max} values of 13.8 (±5.8) and 17.1 (±10.0) ng/mL were obtained for the 4 and 8 mg Norditropin® vials, respectively, at approximately 4 to 5 hr. post dose. The mean apparent terminal $T_{1/2}$ values were estimated to be approximately 7 to 10 hr. However, the absolute bioavailability for Norditropin® after the SC route of administration is currently not known. Norditropin® cartridge formulation is bioequivalent to Norditropin® vial formulation.

INDICATIONS AND USAGE

Norditropin® is indicated for the long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

CONTRAINDICATIONS

Norditropin® should not be used in subjects with closed epiphyses.

Norditropin® should not be used in hypopituitary children who have evidence of actively growing intracranial tumors. Therapy with somatropin should be discontinued if there is evidence of recurrent tumor growth.

Norditropin® should not be used or should be discontinued when there is any evidence of active malignancy. Anti-malignancy treatment must be complete with evidence of remission prior to the institution of growth hormone therapy.

Norditropin® should not be used in any subjects with known hypersensitivity to any of the constituents of the preparation.

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin treated patients (doses 5.3-8 mg/day) compared to those receiving placebo (see WARNINGS).

WARNINGS

Norditropin® cartridges must be used with their corresponding color-coded NordiPen™ delivery device. A Norditropin® cartridge must not be inserted into a pen with a different color code.

See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or with acute respiratory failure. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

PRECAUTIONS

Norditropin® should be used only by physicians with experience in the diagnosis and management of patients with growth hormone deficiency.

Patients with growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process.

Because growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance.

Concomitant glucocorticoid therapy may inhibit the growth promoting effect of Norditropin®. Patients with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth.

A state of hypothyroidism may develop during Norditropin® treatment. Since untreated hypothyroidism may interfere with the response to Norditropin®, patients should have a periodic thyroid function test and should be treated with thyroid hormone when indicated.

Patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital epiphyses more frequently. Any child with the onset of a limp or complaints of hip or knee pain during growth hormone therapy should be evaluated.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products. Symptoms usually occurred within the first eight (8) weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or a reduction of the growth hormone dose. Funduscopic examination of patients is recommended at the initiation and periodically during the course of growth hormone therapy.

Progression of scoliosis can occur in children who experience rapid growth. Because growth hormone increases growth rate, patients with a history of scoliosis who are treated with growth hormone should be monitored for progression of scoliosis.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity, and fertility studies have not been conducted with Norditropin® cartridges.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Norditropin® cartridge formulation. It is also not known whether Norditropin® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norditropin® should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norditropin® is administered to a nursing woman.

ADVERSE REACTIONS

As with all protein drugs, a small percentage of patients may develop antibodies to the protein. Growth hormone antibody with binding capacity lower than 2 mg/L has not been associated with growth attenuation. In some cases, when binding capacity is greater than 2 mg/L, interference with growth response has been observed.

In clinical trials, patients receiving Norditropin® for up to 12 months have been tested for induction of antibodies and 0/358 patients developed antibodies with binding capacities above 2 mg/L. Among these patients, 165 had previously been treated with other preparations of growth hormone and 193 were previously untreated naive patients.

Since antibodies to somatropin have the potential to inhibit further linear growth, only patients failing to respond to treatment should be tested for antibodies.

The following adverse events have been reported from clinical studies: headache, localized muscle pain, weakness, mild hyperglycemia and glucosuria.

Leukemia has been reported in a small number of children who have been treated with growth hormone, including growth hormone of pituitary origin and recombinant somatrem and somatropin. On the basis

of current evidence, experts cannot conclude that growth hormone therapy is responsible for these occurrences. If there is any risk to an individual patient, it is minimal.

Fluid retention and peripheral edema may occur.

OVERDOSAGE
The maximum dose generally recommended should not be exceeded due to the potential risk of side effects.

DOSAGE AND ADMINISTRATION
The Norditropin® dosage and schedule for administration must be individualized for each patient. Generally, subcutaneous administration in the evening, 6-7 times a week, is recommended. It is furthermore recommended to give the injections in the thighs and to vary the injection site on the thigh on a rotating basis. Dosage can be calculated according to body weight.

Generally recommended dosage:
Subcutaneous injection:
0.024 – 0.034 mg/kg body weight, 6-7 times a week.

Norditropin® cartridges must be administered using the NordiPen™ injection pen. Each cartridge size has a color-coded corresponding pen which is graduated to deliver the appropriate dose based on the concentration of Norditropin® in the cartridge.

Measuring the Prescribed Dose:

5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL Norditropin® Cartridges
Each cartridge of Norditropin® must be inserted into its corresponding NordiPen™ injection pen. Instructions for delivering the dosage are provided in the NordiPen™ instruction booklet.

Storage:
Norditropin® cartridges must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

Norditropin® cartridges retain their biological potency until the date of expiry indicated on the label. After a Norditropin® cartridge has been inserted into the NordiPen™ injector, it must be stored in the pen in the refrigerator and used within 4 weeks.

HOW SUPPLIED
Norditropin® 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL cartridges:
Norditropin® is supplied in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL cartridges which must be administered using the corresponding color-coded NordiPen™ injection pen.

Norditropin® 5 mg/1.5 mL cartridge (orange)	NDC 0169-7768-11
Norditropin® 10 mg/1.5 mL cartridge (blue)	NDC 0169-7769-11
Norditropin® 15 mg/1.5 mL cartridge (green)	NDC 0169-7770-11

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Rx Only

For information contact:
Novo Nordisk Pharmaceuticals Inc.
100 Overlook Center, Suite 200
Princeton, New Jersey 08540
USA

Manufactured by:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark